REMARKS

Claims 1-4 and 53-54 are amended. Upon entry of the present amendment, claims 1-4, 6, 15, 16, 50, 51, 53, and 54 are currently pending. The amendments to the claims and specification do not add new matter.

The amendment to claim 1 reciting the phrase "intravenously administering to the patient a β_1-adrenergic blocking agent immediately after surgery" is supported by the specification, such as on page 18, lines 7-11. The amendment to claims 1-4 and 53-54 clarify what Applicant regards as the invention.

Amendments to the Title and Abstract were requested by the Examiner and serve to clarify what Applicant regards as the invention.

Reconsideration is respectfully requested in light of the following remarks.

Interview Summary

Applicant kindly thanks Examiner Spivack for the personal interview conducted on September 7, 2005 in which Applicant's representatives, Albert Halluin and Loreli Westin discussed with the Examiner patentability of pending claims in light of prior art references cited in the Final Office Action.

In the Amended Claims

As amended herein, the claims are drawn to methods comprising *intravenous* administration of a β_1-adrenergic blocking agent *immediately after surgery and administration of the agent daily thereafter* until symptoms of cardiovascular stress are reduced, wherein the β_1-adrenergic blocking agent is administered *near the maximum effective dose* of the agent. Representative β_1-adrenergic blocking agents that can be employed in the claimed methods are described in the present Specification and include, but are not limited to, atenolol, metaprolol, esmolol, acebutolol, practolol, alprenolol, propanolol, nadolol, timolol, pindolol, labetaolol, stoalol, and oxprenolol. *See, e.g.*, Specification at page 7, lines 7-15.

Applicant's invention is drawn, in part, to the surprising discovery that intravenous administration of a near maximum effective dose of a β_1-adrenergic selective blocker *immediately after surgery and daily thereafter* reduces cardiovascular complications. Dr. Dennis Mangano's declaration under Rule 132, previously filed on April 8, 2005, states that beneficial cardiovascular effects are realized when β_1-adrenergic selective blockers are administered to a patient *prior to emergence from anesthesia following surgery.*[1] Furthermore, Dr. Mangano's declaration stated that, at the time of filing, he understood the phrase administration "immediately after surgery" to mean that administration occurs prior to a patient's emergence from anesthesia following surgery.[2]

Intravenous administration of maximum effective doses of a β_1-adrenergic blocker during the period prior to emergence from anesthesia offers significant advantages over the prior art. First, because a patient is still in an anesthetic state immediately after surgery, he or she is unable to swallow and thus, unable to receive a β_1-adrenergic blocker in oral form. By employing the claimed method, the β_1-adrenergic blocker is administered intravenously in the period prior to emergence from anesthesia following surgery to impart beneficial cardiovascular effects. Secondly, therapeutic agents typically exhibit poor bioavailability when administered to a patient in an anesthetic state immediately after surgery. In the claimed methods, a near maximum effective dose of the β_1-adrenergic blocker is administered during this time period.

Rejection Under 35 U.S.C. § 103(a)-Obviousness

Claims 1-4, 6, 15, 16, 50, 51, 53, and 54 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Merrick *et al.* (European Journal of Cardio-thoracic Surgery, 9(3): 146-149 (1995)).

Applicants respectfully traverse the rejection as the teachings of Merrick *et al.* does not teach or suggest the presently claimed methods. Specifically, Merrick *et al.* does not teach or suggest administration of a β_1-adrenergic blocking agent in an amount near the **maximum effective dose**. Additionally, Merrick *et al.* does not teach or suggest **intravenous administration** of a β_1-adrenergic blocking agent. Furthermore, Merrick *et al.* does not teach or suggest administering a β_1-

[1] Mangano Declaration of April 8, 2005, at Paragraph 11.
[2] Mangano Declaration of April 8, 2005, at Paragraph 16.

adrenergic blocking agent in the time period **prior to a patient's emergence from anesthesia following surgery**.

Merrick *et al.* does not teach or suggest administration of a β_1-adrenergic blocking agent in an amount near the maximum effective dose, as is recited in the present claims. According to Merrick *et al.* patients were administered either "propafenone 300 mg twice daily (105 patients) or atenolol 50 mg once daily (102 patients) **orally** for 7 days **after** operation." (Emphases added) Merrick *et al.*, abstract. The near maximum effective dose of atenolol is, on average about 2 mg/kg,[3] and for a patient weighing 78 kg, the near maximum effective dose of atenolol is 156 mg. Furthermore, dependent claim 51 recites that the maximum effective dose of atenolol is 100 mg/day orally or about 10 mg BID intravenously. Therefore, the dosage in Merrick *et al.* is about half of the average maximum effective dose proscribed for atenolol. Merrick *et al.* fails to teach or suggest administration of a near maximum effective dose of a β_1-adrenergic selective blocker.

Merrick *et al.* does not teach or suggest intravenous administration of a β_1-adrenergic blocking agent in the time period prior to a patient's emergence from anesthesia following surgery. Instead, Merrick *et al.* teaches oral administration of atenolol on the first postoperative day. "We limited our study to postoperative oral medication as we wanted to show a useful effect before trying a potentially pro-arrhythmogenic agent during the perioperative period when the patient is often unstable and is receiving anaesthetic and inotropic support." Merrick *et al.*, page 148, column 2, paragraph 3 (emphasis added). Merrick *et al.* fails to teach or suggest intravenous administration of a β_1-adrenergic selective blocker.

Merrick *et al.* does not teach or suggest administration of a β_1-adrenergic blocking agent in the time period prior to a patient's emergence from anesthesia following surgery. Instead, Merrick *et al.* teaches administering propafenone or atenolol after a patient has already emerged from anesthesia following cardiac surgery. "The drugs were administered orally from the first postoperative day (or as soon as the patient was able to take oral medication) until the 7th postoperative day or until an end point was reached." Merrick *et al.*, page 147, column 1, paragraph 2 (emphasis added). "We limited our study to postoperative oral medication as we wanted to show a

[3] See Response of July 5, 2001 at page 9, Paragraph 3 citing Physician's Desk Reference (2001).

useful effect before trying a potentially pro-arrhythmogenic agent during the perioperative period when the patient is often unstable and is receiving anaesthetic and inotropic support." Merrick *et al.*, page 148, column 2, paragraph 3 (emphasis added). Because Merrick *et al.* teaches that study medication is administered orally, it can be deduced that Merrick *et al.* teaches administering propafenone or atenolol after surgery, after the patient has emerged from anesthesia, and not before a patient emerges from anesthesia (*i.e.*, immediately after surgery), as is presently claimed. Moreover, Merrick *et al.* explicitly teaches away from administering an agent "during the perioperative period when the patient is often unstable" in favor of administering atenolol after the patient has completely emerged from anesthesia.

For the foregoing reasons, Applicants respectfully assert that the present claims are non-obvious over Merrick *et al.* because the cited reference does not teach or suggest **intravenous** administration of **a near maximum effective dose** of β_1-adrenergic blocking agent **immediately after surgery** and daily thereafter, as is recited in the present claims.

Accordingly, Applicants respectfully request that the above rejection of claims 1-4, 6, 15, 16, 50, 51, 53, and 54 be withdrawn.

During a telephone discussion on September 13, 2005 between the undersigned attorney and Examiner Spivack, the Examiner raised the question of patentability of the present claims over Kataria et al. (J. Cariothoracic Anesth. (USA) 1990 415 Suppl. 2 (13-16). Kataria et al. has been cited earlier and discussed in the previous responses. While Kataria et al. disclose intravenous (IV) administration of the beta-adrenergic blocker "during the emergence and recovery from anesthesia after general surgery," the reference is defective as a reference for several reasons. First, applicant's method provides for the administration of the beta-adrenergic blocker "prior" to the emergence from anesthesia as opposed to "during emergence" from anesthesia. Second, applicant's method provides for the maximum administration of the beta-adrenergic blocker, whereas Kataria et al. does not employ the maximum dose. Third, Applicant's, method clearly provides for a second follow-on treatment phase by continuing administration of the beta-adrenergic blocker. Kataria et al. does not teach or suggest this second step. In fact, Kataria et al. teaches away from employing this second step by the use of a "fast acting" and "short-lasting" beta-adrenergic blocker. Clearly, Kataria et al.

teaches that one should not continue having the beta-adrenergic blocker present in the patient after surgery – the opposite of the presently claimed invention.

Accordingly, the claims are patentable over Kataria et al.

CONCLUSION

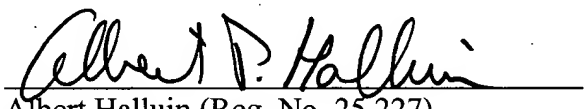
Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 27116-701.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Date: September 14, 2005

By: 

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